

Burden of Respiratory Syncytial Virus–Associated Acute Respiratory Infections During Pregnancy

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Background. With the licensure of maternal respiratory syncytial virus (RSV) vaccines in Europe and the United States, data are needed to better characterize the burden of RSV-associated acute respiratory infections (ARI) in pregnancy. The current study aimed to determine among pregnant individuals the proportion of ARI testing positive for RSV and the RSV incidence rate, RSV-associated hospitalizations, deaths, and perinatal outcomes.

Methods. We conducted a systematic review, following PRISMA 2020 guidelines, using 5 databases (Medline, Embase, Global Health, Web of Science, and Global Index Medicus), and including additional unpublished data. Pregnant individuals with ARI who had respiratory samples tested for RSV were included. We used a random-effects meta-analysis to generate overall proportions and rate estimates across studies.

Results. Eleven studies with pregnant individuals recruited between 2010 and 2022 were identified, most of which recruited pregnant individuals in community, inpatient and outpatient settings. Among 8126 pregnant individuals, the proportion with ARI that tested positive for RSV ranged from 0.9% to 10.7%, with a meta-estimate of 3.4% (95% confidence interval [CI], 1.9%–54%). The pooled incidence rate of RSV among pregnant individuals was 26.0 (95% CI, 15.8–36.2) per 1000 person-years. RSV hospitalization rates reported in 2 studies were 2.4 and 3.0 per 1000 person-years. In 5 studies that ascertained RSV-associated deaths among 4708 pregnant individuals, no deaths were reported. Three studies comparing RSV-positive and RSV-negative pregnant individuals found no difference in the odds of miscarriage, stillbirth, low birth weight, and small size for gestational age. RSV-positive pregnant individuals had higher odds of preterm delivery (odds ratio, 3.6 [95% CI, 1.3–10.3]).

Conclusions. Data on RSV-associated hospitalization rates are limited, but available estimates are lower than those reported in older adults and young children. As countries debate whether to include RSV vaccines in maternal vaccination programs, which are primarily intended to protect infants, this information could be useful in shaping vaccine policy decisions.

Keywords. respiratory syncytial virus; pregnancy; disease burden.

Respiratory syncytial virus (RSV) is a major respiratory pathogen that can cause acute respiratory infections (ARIs) in people of all ages and can infect people multiples times throughout their lives. Severe manifestations disproportionately affect those at the extremes of age, causing a significant disease burden in these population groups [1–3]. Pregnant individuals, with their inherent immunological changes, could be at increased risk of severe RSV infection, but RSV infections in pregnant individuals remain poorly characterized [4]. During pregnancy, maternal RSV antibodies are actively transferred

across the placenta to the fetus and later provide some immunity to infants in the first few months after birth [5, 6]. Higher titers of maternal antibodies, especially against F protein in prefusion conformation, reduce the risk of severe disease in infants [7].

Passive immunization during pregnancy has been used successfully to protect young infants from diseases such as tetanus, pertussis, influenza, and severe acute respiratory syndrome coronavirus 2 [8–11]. Maternal immunization also provides direct benefits to the pregnant individuals by reducing risk of infection and associated complications during the pregnancy and postpartum periods [8–12]. RSV vaccines for pregnant individuals have recently been licensed in the United States and Europe. While the primary goal of antenatal RSV vaccination is focused on providing protection to young infants, antenatal vaccination could also have protective benefits for pregnant individuals and the pregnancy as has been documented for other maternal immunizations [8, 12].

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We conducted a systematic review and meta-analysis of studies that included pregnant individuals with ARI who underwent testing for RSV infection to estimate the proportion of ARI episodes that tested positive for RSV, incidence rates of antenatal RSV infection, and numbers of RSV-associated hospitalizations and deaths. We also characterized RSV-associated perinatal outcomes.

METHODS

We searched articles in 5 databases: Medline (Ovid), Embase (Ovid), Global Health (Ovid), Web of Science, and Global Index Medicus. Search terms that broadly included RSV and pregnant individuals are provided in [Supplementary Table 1](#). The database searches included the period from 1 January 1996 to 24 November 2022, without any language restriction. We also manually searched the reference list of eligible studies identified from databases to identify additional eligible studies.

When published data were insufficient for meta-analysis or when data collection continued after publication, we contacted pharmaceutical companies and observational study authors to obtain additional unpublished data pertinent to our review. We decided a priori that if ≥ 2 published reports were from the same study or if the unpublished data overlapped with the published report, then the data set that provided data for the maximum length of time or provided the most details would be included in the analysis. We registered the systematic review on the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022372847) and followed the PRISMA 2020 reporting guidelines while conducting the review [13].

We included data from observational studies related to pregnant individuals with study-defined ARI who had been tested for RSV by culture, antigen, and molecular testing ([Supplementary Table 2](#)). The definition of ARI varied from study to study. Given the scarcity of data on RSV in pregnant individuals, we broadened our clinical definition criteria and included influenzalike illness and severe ARIs. We excluded studies not focused on pregnant individuals, studies in which clinical specimens were not laboratory tested for RSV, conference abstracts, reviews, and case reports. We developed and piloted a data extraction template. The literature search, study selection and data extraction were carried out independently by 2 reviewers (H. M. and S. K.). Any disagreements were resolved through mutual discussion or with the help of an arbiter (H. N.).

Risk of Bias and Data Analysis

The risk of bias in the included studies was assessed using the Joanna Briggs Institute scale ([Supplementary Table 3](#)). Data analyses were conducted using R software, version 4.0.3 [14]. We used a random-effects meta-analysis to estimate the

proportion of pregnant individuals with ARI who tested positive for RSV and the RSV incidence rate among pregnant individuals. When necessary, we converted the incidence rates from person-months to person-years by multiplying the person-months by 12.

Subgroup analyses were performed based on the case identification settings and whether the study period was seasonal or throughout the year. Seasonal studies were defined as those conducted during RSV epidemic periods, which typically occur from October to May in temperate regions and at different times in tropical regions [15]. An evaluation of publication bias was conducted using funnel plot asymmetry and a weighted Egger's regression test with a threshold of 0.05 [16]. For the proportion positive among pregnant individuals with ARI, we did a sensitivity analysis that involved excluding a single study at a time to evaluate its influence on the overall outcome [17]. We described in pregnant individuals the RSV-associated hospitalization rate, the proportion hospitalized among pregnant individuals with RSV-associated ARI, the proportion with RSV infection among pregnant individuals with ARI-associated hospitalizations, and the number of RSV-associated deaths among those with ARI.

We used random-effects meta-analysis to determine the proportions of specific perinatal outcomes among pregnant individuals with RSV-associated ARI: preterm birth (birth before 37 weeks' gestational age), low birth weight (<2500 g), stillbirth, and miscarriage. The cutoff point for miscarriage and stillbirth was 20 weeks' gestational age, with miscarriage defined as spontaneous loss of pregnancy before 20 weeks and stillbirth as death of the fetus at or after 20 weeks. We also estimated using random-effects meta-analysis the association between RSV infection and perinatal outcomes.

RESULTS

Study Selection

A search of databases yielded a total of 630 records ([Supplementary Figure 1](#)). Among these, 602 were excluded as they did not meet the eligibility criteria, leaving 28 full-text articles for further assessment. Of these 28 studies, 22 were excluded and 2 additional records were identified through citation searching. We did not include any unpublished data from the placebo arm of recent phase II/III RSV maternal vaccine trials as they did not follow up pregnant individuals for ARI or test them for RSV (Pfizer PF-06928316); the phase III trials were conducted during the coronavirus disease 2019 (COVID-19) pandemic when RSV activity in general was very low across most sites (Pfizer and GlaxoSmithKline [GSK] RSV MAT-009), and recruitment was halted midway following a recommendation by the independent data monitoring committee (GSK). We also did not include data from phase III Novavax RSV M-301 because ascertainment of RSV disease

in the pregnant individuals was passive and the number of individuals positive for RSV-ARI was in the low single digits.

Unpublished data were made available by the authors of 3 additional observational studies. We excluded 1 previously published article that met the inclusion criteria owing to its overlap with unpublished data [18]. Finally, a total of 11 studies (8 published and 3 unpublished) were included in the analysis for this systematic review [19–26].

Study Characteristics

The recruitment period of pregnant individuals in the included studies ranged from 2010 to 2022 (Supplementary Table 4). Except for RSV-associated deaths, all other estimates are based on data collected during the pre-COVID-19 pandemic era. Of all 11 included studies, 8 were cohort and 3 were cross-sectional studies. Six studies were conducted in high-income countries (Australia, Canada, Israel, Panama, and the United States), 4 in lower-middle-income countries (El Salvador, Kenya, Mongolia, and Nepal), and 2 in upper-middle-income countries (South Africa and Thailand). Four studies were conducted year-round, lasting between 2 and 6 years, and 7 were conducted seasonally, lasting from 1 to 8 seasons. One study reported data exclusively among outpatients, 2 studies exclusively among inpatients, and 3 studies exclusively in the community. Of studies with a combination of settings, 3 were in the community, outpatients, and inpatients, and 2 were in outpatients and inpatients.

Seven studies used ARI as the primary definition for inclusion. Meanwhile, other studies used varying definitions that included criteria like RSV positive, limiting to only febrile patients with ARI or including specific subpopulations, such as those living with human immunodeficiency virus (HIV) infection. The RSV diagnostic test used in most of the studies was polymerase chain reaction (9 studies), with other methods including culture, antigen tests, and rapid diagnostic tests. Of studies that provided information about clinical specimen types, 4 collected nasal swab samples; 3, nasopharyngeal swab samples; and 1, oropharyngeal swab samples. Of 5 studies with gestational age reported, 1 included pregnant individuals in all 3 trimesters, 3 in the second and third trimesters, and 1 in the first and second trimesters.

Risk of Bias of Included Studies

The cohort studies presented a low risk of bias, with all studies achieving scores of $\geq 82\%$ according to Joanna Briggs Institute assessment tools (Supplementary Table 5) [19–21, 24–26]. Cross-sectional studies by Hause et al in 2018 [22] and 2021 [23] also displayed low risk of bias, with scores of 88% and 75%, respectively (Supplementary Table 6).

Proportion of Pregnant Individuals With RSV-Positive ARIs

Supplementary Table 7 presents the proportion of pregnant individuals with ARI who tested positive for RSV among studies

that tested in community, outpatient, or inpatient settings. These studies were conducted in Africa (Kenya and South Africa) [24, 25], Central America (El Salvador and Panama), North America (United States) [19, 22, 23], South-East Asia (Nepal and Thailand) [21], and the Western Pacific (Mongolia) [20]. There were 203 cases of RSV infection among 8126 pregnant individuals tested, with the proportion of positive cases ranging from 0.9% in HIV-uninfected persons in South Africa to 10.7% in an unpublished study in Thailand. The pooled proportion of RSV positivity in pregnant individuals with ARI was 3.4% (95% confidence interval [CI], 1.9%–5.4%) (Figure 1).

After each study was removed sequentially from the meta-analysis, the overall estimates ranged from 2.2% (95% CI, 1.3%–3.2%) to 4.1% (2.1%–6.2%) (Supplementary Table 8). The Egger's test indicated publication bias ($P = .046$). A visual inspection of the funnel plot did not reveal marked asymmetry to conclusively support the Egger's test result (Supplementary Figure 2). In studies conducted during RSV seasons the prevalence was 4.4% (95% CI, .8%–10.1%), while in year-round studies, it was 2.5% (1.3%–4.0%), a statistically significant difference ($P < .001$) (Supplementary Figure 3). The proportion of pregnant individuals positive for RSV was 9.8% (95% CI, 4.3%–18.5%) among outpatients, 5.5% (.6%–14.0%) among community participants, 3.6% (.3%–8.8%) among outpatients and inpatients, and 1.7% (.8%–2.7%) among community, outpatient, and inpatient participants (Supplementary Figure 4).

Incidence Rate of RSV in Pregnant Individuals

Supplementary Table 9 presents the incidence rate of RSV among pregnant individuals. The included studies were conducted in Kenya [25], South Africa [24], Thailand, and Mongolia [20]. All studies identified pregnant individuals across community, inpatient and outpatient settings, except unpublished data by Dawood for which participants were identified only in the community in Thailand. The incidence rate of RSV varied from 0.2 per 1000 person-months among pregnant individuals in an unpublished study from Thailand to 24.0 per 1000 person-months in Mongolia. The RSV incidence rate meta-estimate in pregnant individuals with diagnosed ARI was 2.1 (95% CI, 1.3–3.0) per 1000 person-months. The incidence rate was 1.7 (95% CI, 1.0–2.3) per 1000 person-months in seasonal studies and 4.9 (.3–9.5) per 1000 person-months in year-round studies, a significant difference ($P = .17$) (Figure 2).

RSV-Associated Hospitalizations in Pregnant Individuals

RSV-associated hospitalizations in pregnant individuals were provided in 10 studies; 2 reported hospitalization rates [19] (Dawood, unpublished data), 5 the proportion hospitalized among those with RSV-associated ARI episodes [21, 22, 24, 25] (Frivold, unpublished data), and 3 the proportion of ARI

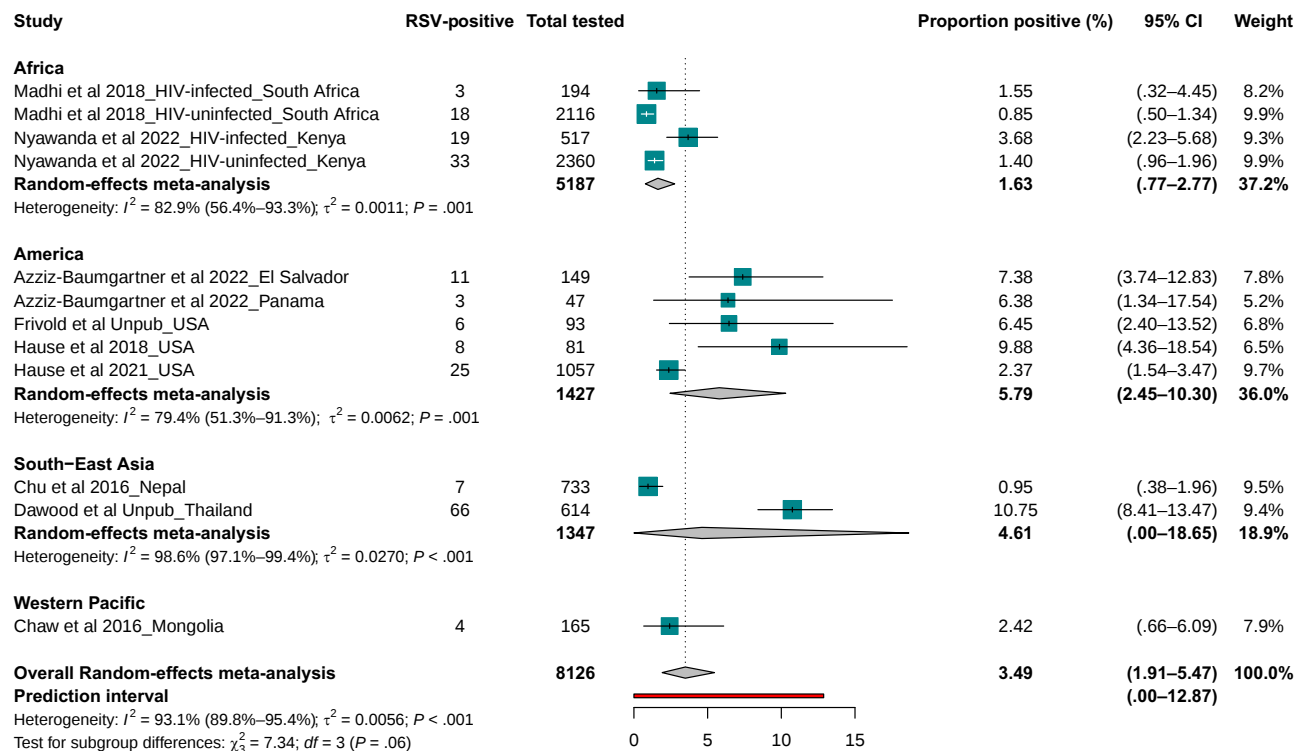


Figure 1. Proportion positive for respiratory syncytial virus (RSV) in pregnant individuals with acute respiratory infections. Published sources in Figure 1 include Madhi et al [24], Nyawanda et al [25], Azziz-Baumgartner et al [19], Hause et al [22], Hause et al [23], Chu et al [21], and Chaw et al [20]. Abbreviations: CI, confidence interval; Unpub, unpublished.

hospitalizations associated with RSV infection [20, 26] (Dawood, unpublished data).

One study conducted in El Salvador reported an RSV hospitalization rate of 3.0 per 1000 person-years among pregnant individuals (Supplementary Table 10) [19]. In an unpublished study from Thailand, a single case of RSV hospitalization was observed in a pregnant person and when extrapolated to the cohort population resulted in a hospitalization rate of 2.4 (95% CI, .4–17.3) per 1000 person-years.

In a study by Hause and colleagues in the United States [22], of 8 pregnant individuals with outpatient, medically attended ARI who tested positive for RSV, 1 required hospitalization (Supplementary Table 11). In other studies, from South Africa [24], Kenya [25], Nepal [21], and the United States (Frivold, unpublished data), in which 6853 individuals were tested, 86 were RSV positive, and no RSV-positive pregnant individuals were hospitalized.

Three studies report data on the proportion of pregnant individuals hospitalized with ARI who tested positive for RSV (Supplementary Table 12) [20, 26]. These studies reported data from Mongolia, Thailand, and a multicountry study across Australia, Canada, Israel, and the United States. The RSV positivity among pregnant individuals hospitalized with ARI ranged from 0% in the study in Mongolia to 9.1% in the unpublished study in Thailand.

RSV-Associated Deaths in Pregnant Individuals With ARIs

We included 5 studies (from Mongolia, Nepal, the United States, and Kenya) that reported data on 4708 pregnant individuals tested for RSV, of whom 203 were RSV positive [20, 21, 26] (Frivold, unpublished data; Havers, unpublished data) (Supplementary Table 13). No deaths were reported among these pregnant individuals.

Perinatal Outcomes in Pregnant Individuals With RSV-Associated ARIs

Three studies conducted in Nepal, Thailand, and South Africa reported data on perinatal outcomes among pregnant individuals who tested positive for RSV [21, 24] (Dawood, unpublished data) (Figure 3 and Supplementary Table 14). The RSV-positive pregnant individuals had 7 infants with low birth weight (6.0% [95% CI, 1.0%–13.4%]) and 12 preterm births (12.3% [5.4%–20.8%]). Two studies provided data on small-for-gestational-age births, stillbirths, and miscarriages. Of the pregnant women who tested positive for RSV in these studies, 5 delivered small-for-gestational-age infants (5.1% [95% CI, .4%–13.0%]), but no miscarriages or stillbirths were reported. Stillbirths, small-for-gestational-age infants, miscarriage, and low birth weight did not differ by antenatal RSV infection status in 3 studies. There was significant difference in the odds of preterm birth between RSV-positive and RSV-negative pregnant individuals (odds ratio, 3.6 [95% CI,

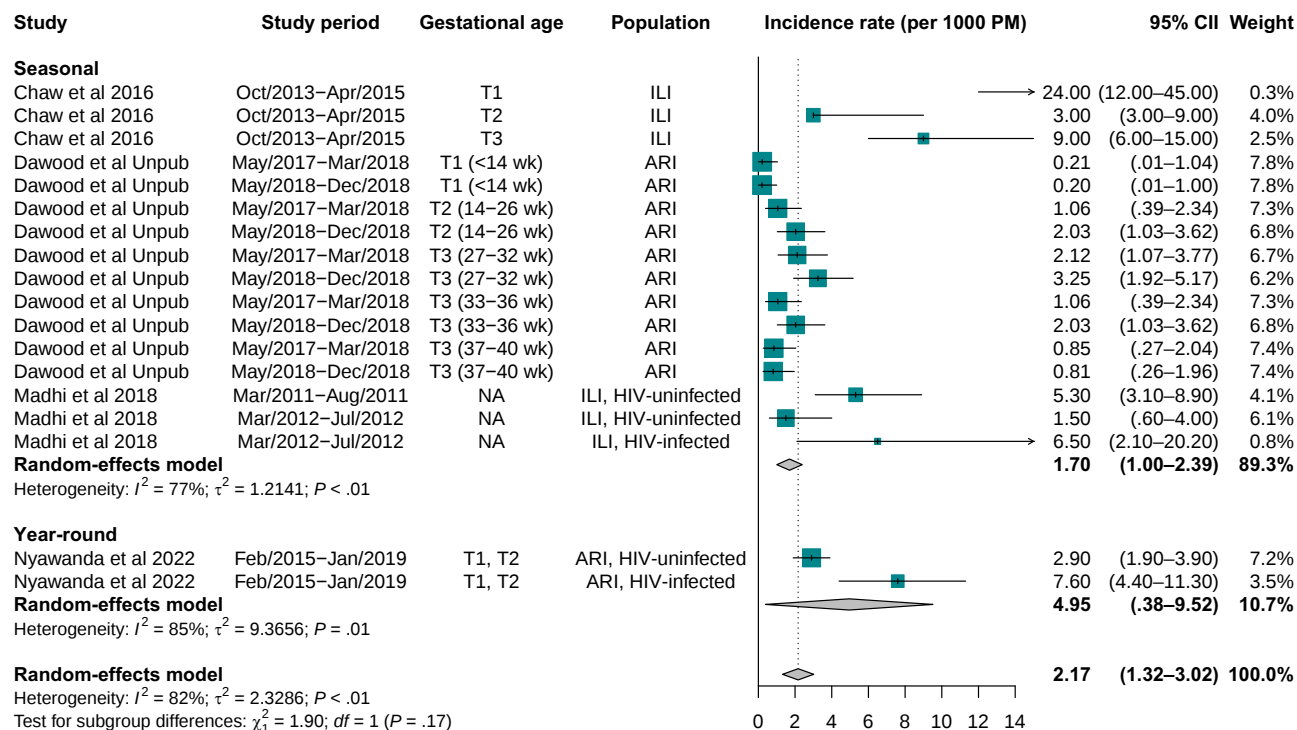


Figure 2. Incidence rate of respiratory syncytial virus (RSV) in pregnant individuals. Published sources in Figure 2 include Chaw et al [20], Madhi et al [24], and Nyawanda et al [25]. Abbreviations: ARI, acute respiratory infections; CI, confidence interval; HIV, human immunodeficiency virus; ILI, influenzalike illness; NA, not available; PM, person-months; T1, first trimester; T2, second trimester; T3, third trimester; Unpub, unpublished.

1.3–10.3)); however, these are based on data from a single study (Dawood, unpublished data).

DISCUSSION

This is the first study to summarize available evidence and quantify RSV-associated ARI burden among pregnant individuals, a population subgroup in whom the RSV burden is poorly understood. We found that 3.4% (95% CI, 1.9%–5.4%) of ARI episodes among pregnant individuals were associated with RSV infection. The estimated incidence rate of antenatal RSV infection was 2.1 (95% CI, 1.3–3.0) per 1000 person-months or 26.0 (15.8–36.2) per 1000 person-years. RSV-associated hospitalizations were uncommon, and no RSV-associated deaths were observed. Based on limited data from 3 studies, the odds of stillbirths, miscarriage, low birth weight, and small size for gestational age did not differ between pregnant individuals who had antenatal RSV infection and those who did not, but antenatal RSV infection was associated with increased odds of preterm delivery (3.6 [1.3; 10.3]).

The paucity of data about the epidemiology of RSV among nonpregnant adults of reproductive ages limits comparisons of RSV incidences rates between nonpregnant and pregnant individuals. We estimated that the incidence of RSV was 26.0 per 1000 person-years in pregnant individuals, which is

comparable to incidence rates reported among adults aged ≥ 18 years with underlying medical conditions or older adults aged ≥ 60 years [27, 28]. For adults ≥ 18 years with cardiopulmonary diseases, the incidence rate of RSV during the epidemic period was 19.1 cases per 1000 person-years [27]. In immunodeficient patients aged ≥ 18 years, a higher incidence rate was observed when studies covered the whole year (36.8 cases per 1000 person-years), and this increased 7-fold when restricted to the epidemic period (260.8 cases per 1000 person-years).

The proportion of pregnant individuals with ARI who were RSV positive was found to be 3.4%, which is similar to findings in previous studies of adults aged ≥ 16 years [28–30]. Based on these numbers, the proportion of ARI cases positive for RSV among pregnant individuals lies between that of adults aged ≥ 16 years with community-acquired pneumonia (2% [95% CI, 1%–3%]) and that of adults with comorbid conditions [11% [7%–16%]] [27, 31].

Limited data on RSV-associated hospitalizations suggest hospitalization rates of 2.4 and 3.0 per 1000 person-years, substantially higher than rates for the 50–64-year age group in both high-income and low- and middle-income countries (0.2 and 0.3 per 1000 person-years, respectively) [31]. However, limited data and different testing and hospital admission practices among pregnant compared with nonpregnant individuals may lead to biased estimates.

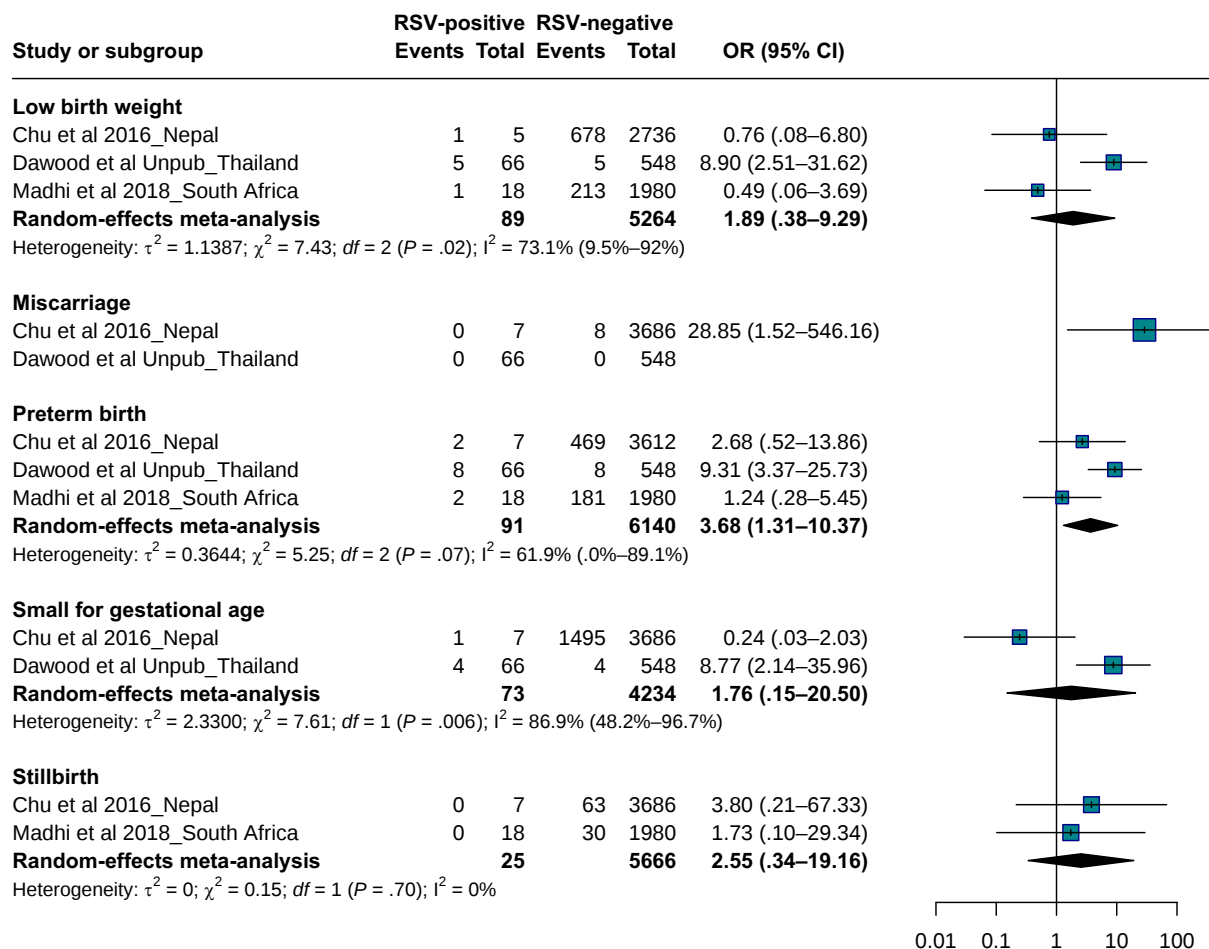


Figure 3. Perinatal outcomes among pregnant individuals with and without respiratory syncytial virus (RSV). For Chu et al [21], low birth weight was available for 5 infants born in RSV-positive groups and 2736 born in RSV-negative groups. Preterm birth was available for 7 infants born in RSV-positive groups and 3612 babies born in RSV-negative groups. Published sources in Figure 3 include Chu et al [21] and Madhi et al [24]. Abbreviations: CI, confidence interval; OR, odds ratio; Unpub, unpublished.

Among prospective studies included in this meta-analysis, only a single hospitalization event was observed among RSV-positive pregnant individuals with ARI, aligning closely with findings in those >60 years old (0.1%) and substantially lower than in RSV-infected adults aged ≥ 18 years with comorbid conditions (32% [95% CI, 23%–43%]) and RSV-infected immunodeficient patients aged ≥ 18 years (38.3% [29%–48%]) [27, 32]. The proportion of RSV-positive cases among hospitalized pregnant individuals with ARI varied broadly, from 0% to 9.1%, aligning with proportions among elderly individuals in high-income countries (6.1%) [2].

There were no reported deaths in the 5 contributing studies on RSV during pregnancy, a lower rate of deaths than in previous meta-analyses that demonstrated varying case fatality rates among adults aged ≥ 18 years or adults with comorbid conditions, ranging between 1.4% and 11.0% [2, 27, 28, 32]. In addition, observational studies have also reported RSV-related deaths in hospitalized young adults [33–35].

Severe illnesses from respiratory infections like COVID-19 and influenza in pregnant individuals, particularly those requiring hospitalization, have been associated with an increased risk of numerous adverse outcomes [36–41]. Specifically, in the case of severe COVID-19 illness, there is an increased risk of preterm birth, fetal growth restriction, postpartum hemorrhage, and stillbirth [36, 38, 39, 41]. Similarly, severe illness from influenza during pregnancy, especially pandemic A/H1N1 influenza, is linked with a greater risk of adverse perinatal outcomes such as preterm birth [37, 40]. In this meta-analysis, among those who were RSV infected during pregnancy, adverse perinatal outcomes include low-birth-weight infants (6.0% [95% CI, 1.0%–13.4%]), preterm infants (12.3% [5.4%–20.8%]) and small-for-gestational-age infants (5.1% [4%–13.0%]); however, the rates were comparable to those in the general populations of the countries where the studies were conducted [42–44]. The only exception was observed in the Nepal study, where preterm births among people with

RSV in pregnancy exceeded the rate seen in the general population [45].

It is important to view the interpretation of these findings within the context of several limitations. Seven of 11 studies tested for RSV only during the epidemic months, and 1 was confined to a single season. Some were not explicitly oriented toward the RSV season, while others were aimed at the influenza season, which does not always coincide with the RSV season and thus might not fully capture RSV disease burden [46, 47]. Furthermore, in most regions, RSV has seasonal circulation patterns, and studies conducted during the perceived RSV season are expected to yield a higher proportion positive [48]. The limited number of studies, reflected in publication bias, coupled with their small sample sizes may lead to potentially imprecise estimates. Notably, we lack adequate data to stratify our estimates by income region, study settings, clinical definition of ARI, or gestational age. We acknowledge the scarcity of consistent data on pregnant individuals with or without RSV or lower respiratory tract infection and the absence of a comparable nonpregnant control group of the same age.

The varied methods and risk factors across the included studies raise concerns about the potential for coincidental similarities in outcome frequencies. In this analysis, we were unable to control for potential confounders such as age, socioeconomic status, and smoking exposure, which could be explored in an individual patient data meta-analysis if data on potential confounders were available. Limitations also arose from laboratory testing, as most included studies relying solely on polymerase chain reaction testing of a single type of upper respiratory tract specimen, which could underestimate the true RSV burden, indicating the need for including serology tests in future research [49, 50]. The clinical case definitions for ARI used in the individual studies, along with the exclusion of nonfebrile cases in some studies, could lead to further underestimation of RSV prevalence [51]. RSV proportion might also be underestimated owing to the lack of clarity surrounding standard of care testing practices in pregnant individuals.

Our current understanding of RSV in pregnant individuals is based on a limited number of studies and participants, indicating the need for more studies. Placebo arms of future phase III maternal RSV vaccine trials could provide valuable RSV burden data through comprehensive prospective disease surveillance of pregnant individuals as well as their infants (as opposed to infants alone). Postlicensure studies of RSV vaccine effectiveness could also offer valuable insights into RSV-associated outcomes among unvaccinated pregnant individuals. Alongside increased testing for RSV in pregnant individuals with ARI, these approaches are crucial to capturing both the burden of RSV and the potential public health impact of maternal vaccines accurately.

The adoption of standardized case definitions, testing, and reporting criteria through improved surveillance will facilitate

more robust estimates of RSV disease burden in pregnant individuals. Further research could examine multiple pathogens, which would allow differentiation between RSV monoinfections and codetection with other viruses. This advancement seems achievable, given the broader adoption of multiplex testing in response to the COVID-19 pandemic.

In conclusion, the RSV incidence rates in pregnant individuals may be comparable to those observed in adults aged 18–49 years with comorbid conditions. Compared with the incidences in older adults or young children, the incidence of RSV-associated severe disease, particularly hospitalizations in pregnant individuals, appears to be lower. For an accurate and reliable assessment of both RSV-associated hospitalizations and deaths in pregnant individuals, more comprehensive research in this area is critical, given the limited data available. Without further analyses comparing RSV-positive versus RSV-negative or ARI versus non-ARI groups, we are unable to draw conclusions from our findings at this point for potential correlations between RSV infection during pregnancy and perinatal outcomes. With the rollout of maternal RSV vaccines due to begin this autumn, these results underscore the need for ongoing research to ensure a comprehensive understanding of the burden of RSV in pregnant individuals.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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